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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,870	11/16/2005	Benny Bang-Andersen	435-US-PCT	2040

45821 7590 03/05/2007

LUNDBECK RESEARCH USA, INC.
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EXAMINER	
O DELL, DAVID K	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,870	BANG-ANDERSEN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell, Ph.D.	1609	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18 and 20-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18 and 20-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16, 18, 20-34 are pending in the current application.

2. This application is a national stage of PCT No. PCT/DK04/00241, filed April 2, 2004 which claims the benefit of U.S. Provisional Application No. 60/460,265, filed April 4, 2003 which claims the benefit of foreign priority under 35 U.S.C. §119(a)-(d) of Danish Application No. PA 2003 00519, filed April 4, 2003.

Objections

3. The disclosure is objected to because of the following informalities: Applicant is referring to "acidic acid" in experimental procedures. The Examiner has assumed that applicant has meant "acetic acid"; this error is repeated throughout the specification, a portion of pg. 28 is shown below. Appropriate correction is required.

A mixture of *tert*-butyl 4-[2-(2,4-dimethylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate (0.5 g) and a mixture of acidic acid and conc. hydrochloride acid (3:1)

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-14, 16, 18, 20-34 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-11 of U.S. Patent No. 7,144,884 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '834 patent clearly claims the Markush of the instant case as well methods of using the compounds in the treatment of depression and various disorders.

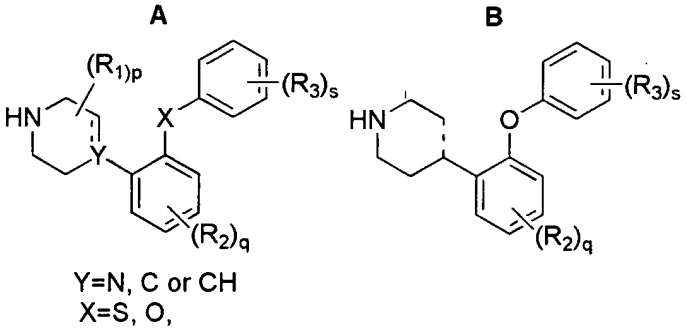


Figure 1. Applicant's previously patented compounds **A** vs. the compounds of the instant application **B**.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) The prior art (the '884 patent) discloses the compounds of the instant case by its Markush claims 1 and 7. In this case structure **A** of Figure 1 applicant has not defined Y or X in claim 1 and thus we must see these as being the definitions of the specification as delineated in Figure 1 (Y=N, C or CH; X=S or O). Claim 7 still fails to define Y, but lets us know that X=O or S.

B) The generic structure of the '884 patent **A** and the generic structure of the instant case **B** clearly overlap, see Figure 1. The prior disclosed invention encompasses the instant claims at hand.

C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '884 patent.

D) Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the

claims presented..... ..Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See In re Borcherdt et al., 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in Ex parte Robinson, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents. Please note that the individual compounds of the invention are not being rejected here, it is only the Markush claim and all dependent claims that are at issue here.

5. Claims 1-12, 14, 16, 18, 20-34 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8-17 of U.S. Patent No. 7,138,407 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '407 patent clearly claims the same Markush of the instant case as well methods of using the Markush compounds in the treatment of depression and various disorders. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) The claims of the '407 patent discloses the generic structure via Markush structure **A** (Figure1). In this case Y= C, X may be O or S.

B) There is little difference between the generic structure of the '407 patent and the generic structure of the instant case, see Figure 1. In the '407 patent the Y group is C and the unspecified bond is a double bond, this is just the same as the instant case where a double bond is in the piperidine ring, X may be O or S (structure **A** Figure 1). In the instant case applicant has claimed both the single and double bond and of course X=O S (structure **B** Figure 1). Thus the Markush of the instant case are clearly contained in the prior filed applications Markush.

C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '884 patent.

D) Considering the evidence at hand here an obviousness type double patenting rejection is appropriate. Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... ..Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See In re Borcherdt et al., 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94

USPQ 175 , and the cases collected in Ex parte Robinson, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents in what would be identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

6. Claim 1-14, 16, 18, 20-34 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 4-10, 12-14, 17, 19, 21, 23, 25, 27, 29, 31-34 of copending Application No. 11/551,188. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. co-pending U. S. Application 11/551,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '238 patent clearly claims the Markush of the instant case as well methods of using the compounds in the treatment of depression and various disorders. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) The prior art (the '238 patent) discloses the Markush structure **A** Figure 1, Y=CH, and X=S or O.

B) There is little difference between the Markush claims of the '238 patent and the instant case, see Figure 1. In the '238 patent the Y group is CH and the unspecified bond is single, this is just the same as the instant case where a single bond is in the piperidine ring (structure **B** Figure 1). The instant claim encompasses the prior filed application in part and vice versa.

C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '238 patent.

D) Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... ..Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See In re Borcherdt et al., 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in Ex parte Robinson, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene

as solvents in what would be identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

Considering the evidence at hand here an obviousness type double patenting rejection is appropriate. Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... ..Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See In re Borcherdt et al., 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in Ex parte Robinson, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents in what would be identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

Claim Rejections - 35 USC § 112

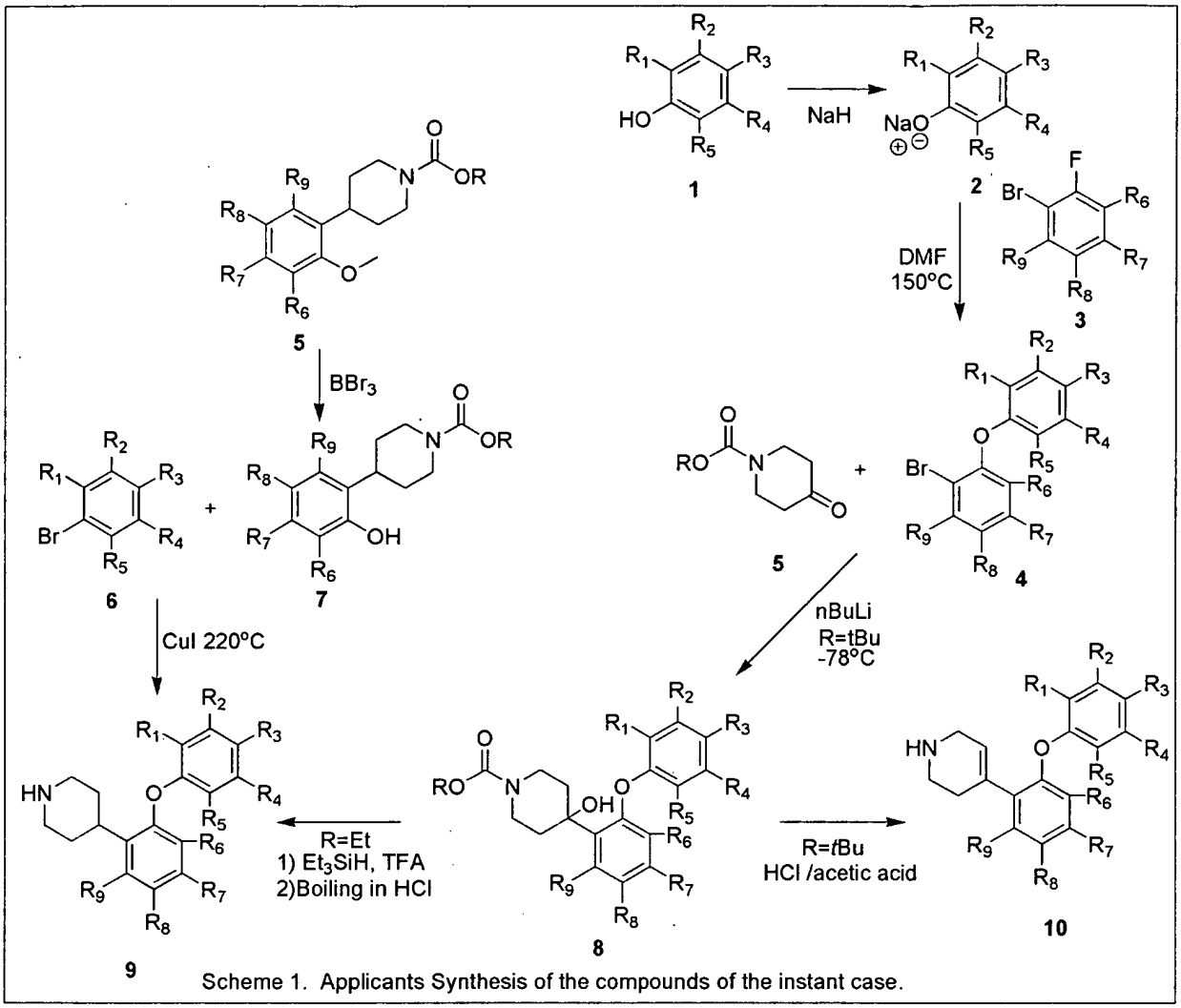
The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-14, 16, 20-31 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain substituents R_1-R_8, it does not reasonably provide enablement for the exhaustive list given. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The availability of the starting material that is needed to prepare the invention as claimed will be discussed first. As per MPEP:

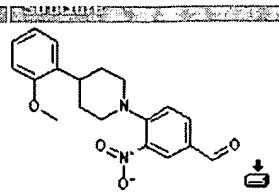
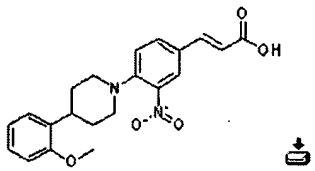
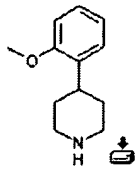
> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. **The same can be said if certain chemicals are required to make a compound or practice a chemical process.** In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

A reconstruction of applicant's synthesis has been provided for clarity and is shown as Scheme 1.



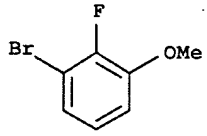
Scheme 1. Applicants Synthesis of the compounds of the instant case.

The substituents R_6-R_9 cited in the claims depend from the availability of the 2-piperidyl-anisoles **5** and the 1-bromo-2-fluoro-benzenes **3**. While applicants only working example is with **5** where R_6-R_9=H, no other such compounds are commercial (as below from the Maybridge online catalog). Thus **5** is not a source of any substituents other than H.

4-[4-(2-methoxyphenyl)piperidino]-3-nitrobenzaldehyde, 97%	301334-92-9	
3-{4-[4-(2-methoxyphenyl)piperidino]-3-nitrophenyl}acrylic acid, 97%	301334-95-2	
4-(2-methoxyphenyl)piperidine, 97%	58333-75-8	

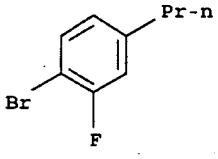
The other source of diversity for R_6-R_9 are the 1-Bromo-2-Fluorobenzenes **3**, only a handful are commercial, a list is provided below, with Registry #'s.

295376-21-5

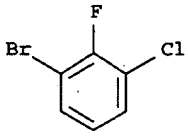


,1-bromo-2-fluoro-3-methoxy Benzene

167858-56-2

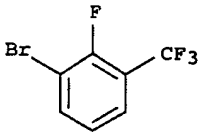


144584-65-6



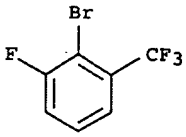
1-bromo-3-chloro-2-fluoro-Benzene

144584-67-8



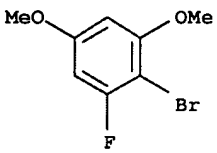
1-bromo-2-fluoro-3-(trifluoromethyl)- Benzene

104540-42-3



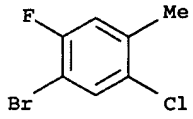
2-bromo-1-fluoro-3-(trifluoromethyl)- Benzene

206860-47-1



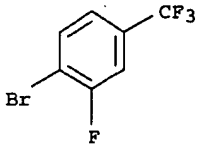
2-bromo-1-fluoro-3,5-dimethoxy- Benzene

93765-83-4



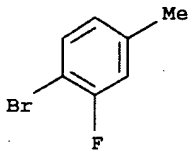
1-bromo-5-chloro-2-fluoro-4-methyl- Benzene

40161-54-4



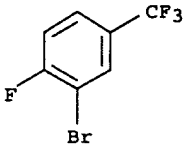
1-bromo-2-fluoro-4-(trifluoromethyl)- Benzene

452-74-4



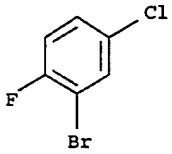
1-bromo-2-fluoro-4-methyl-Benzene

68322-84-9

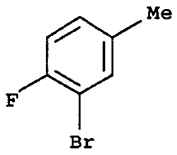


,2-bromo-1-fluoro-4-(trifluoromethyl)- Benzene

1996-30-1

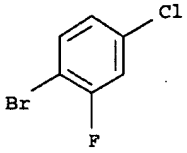


452-62-0

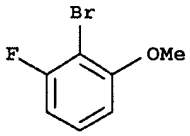


2-bromo-1-fluoro-4-methyl-benzene

1996-29-8

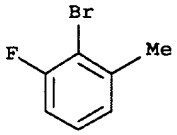


446-59-3



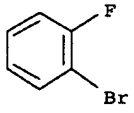
,2-bromo-1-fluoro-3-methoxy-Benzene

59907-13-0



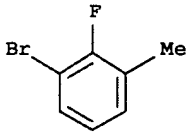
2-bromo-1-fluoro-3-methylbezene

1072-85-1



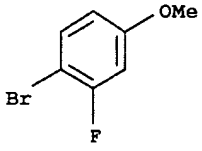
1-bromo-2-fluoro- Benzene

59907-12-9



1-bromo-2-fluoro-3-methyl-benzene

458-50-4



1-bromo-2-fluoro-4-methoxy-Benzene

The limitations inherent in the chemistry used to prepare the compounds of the instant case will be discussed in relation to the substituents R_1-R_9. The reaction of sodium phenolates **2** with 1-bromo-2-fluoro-benzenes **3** to yield the diaryl ethers **4** has several limitations as to what substituents are tolerated. The substituents R_1-R_5 needs to be an electron rich substituents (preferably *o* or *p* to the phenolate oxygen), and the 1-bromo-2-fluoro-benzenes **3** (the groups R_6-R_9) should possess electron withdrawing groups (see March, J. *Advanced organic chemistry*, **1985**, 589), the later limitation is inherent to the starting material and won't be discussed further, as no access is available to the long list of substituents listed (see above). It is somewhat surprising that such remarkable regioselectivity is obtained, as the Br is well known to react is such reactions (see March, J. *Advanced organic chemistry*, **1985**, 589), however the rate of reaction of the F substituents must be significantly higher. The most disturbing examples in the instant case are listed as "halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, halo alkyl, " which will give cyclic ethers via the well known Williamson ether synthesis March pg. 342-343. In addition alkynes and alkenes where R_1-R_9 is "C1-6-alk(en/yn)yl, C1-6-alk(en/yn)yloxy, C1-6--alk(en/yn)ylsulfanyl, hydroxy-Cl-6--alk(en/yn)yl, halo-C1-6-alk(en/yn)yl, halo-C1-6--alk(en/yn)yloxy, Cl-6-alk(en/yn)yl, cyano-C_{1-8}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-Cl_s-alk(en/yn)yl, and NR_ZR_W-C1-6-alk(en/yn)yl, wherein Rz and Rw are independently C_{1-8}-alk(en/yn)yl, C_{3-8}- cycloalk(en)yl, and C_{3-8}-cycloalk(en)yl-Cl.s-alk(en/yn)yl" will undergo addition of phenolates as is well known (March *Advanced organic chemistry* pg. 684-685.) Of course we have no idea where these starting materials came from. If

this alkyne is terminal it will be deprotonated. Even if such starting materials could be shown to provide the requisite groups, applicants conditions for the reaction will promote intramolecular cyclization of the phenol oxygen onto pendant olefins and alkynes in the ortho position as is well known in the art. Hurd et. al. *J. Am. Chem. Soc.* **1940**,*5*, 212-222, entire document) teach that olefins react to give chromans under acidic conditions (applicant "boils" compounds in acid in subsequent steps). Buckle et. al *J. Chem. Soc. Perkin Trans. 1* **1985**, 2443-2446 entire document; teaches that phenolate anions with pendant alkynes will produce benzofurans.

The addition of the organolithium generated from metal-halogen exchange of the aryl bromide **4**, and its reaction with piperidin-4-one **5** will be discussed next. Surprisingly "halogen" is claimed in the Markush group. "Halogen" includes iodine, and iodine preferentially undergoes metal-halogen exchange over bromide, as is taught by Dabrowski et. al. *Tetrahedron*, **2005**, 6590-6595, pg. 6991, Table 1, entry 5. Applicant has provided conditions, low-temperature that might limit Parham type cyclizations, but the olefin or alkyne is susceptible to attack by aryl lithiums. These reactions become extremely complex when substituents listed as "halo-C1_6-alk(en/yn)yl, halo-C1s-alk(en/yn)yloxy, halo alkyl," are included and would include intramolecular metal-halogen exchange, formation of vinyl lithiums and numerous other reactions, (such reactions are discussed in detail in Clayden, J. *Organolithiums: Selectivity for Organic Synthesis 2002,* Pergamon: New York, Chapter 3, 111-148). Applicant's claim to "Cl_6-alk(en/yn)ylsulfanyl" and other acid functional groups could result in preferential deprotonation over metal-halogen exchange and such reactions require very controlled

conditions such as lack of stirring and even then may not function as desired (Clayden, ibid.). In addition to these limitations Parham teaches that "cyano" or nitrile in the ortho position will give rise to spiro-cyclic benzofurans when aryl lithiums such as **4** react with ketone electrophiles such as **5** (Parham, et. al. *J. Org. Chem.* **1976**, 41, 1187-1191, Table 1 compound **8** to compound **9** via cyclohexanone). The other nitrile containing groups "cyano-C_{1-8}-alk(en/yn)yl" give extremely complex mixtures and as stated by Parham himself (ibid. pg. 1189).:

> "When the alkylnitrile function in the arene is not benzylic, then halogen-metal exchange occurs readily (Scheme III). While the primary reaction of **24** with 1 equiv of *n*-butyllithium is anion formation at the methylene group adjacent to the nitrile function, the anionic center is sufficiently removed to permit complete halogen-metal exchange with the second equivalent of n-butyllithium. **Such reactions are not, however, of synthetic interest** since there are two anionic centers available for reaction with E+. Such reactions are further complicated by the fact that appreciable butylation occurs (**26** and **27**) even at -100°C. It is also of interest to note that iodine-lithium exchange is sufficiently more rapid than bromine-lithium exchange to permit appreciable halogen-metal exchange in **28** (80%) in preference to proton removal with only 1 equiv of n-butyllithium (eq 2, Scheme III); however, attempts to elaborate **29** and/or **30** formed from **28** and 1.5 equiv of n-butyllithium at -100°C, with cyclohexanone, led to a complex unresolved mixture containing butylated products." (emphasis added).

The other route given for the construction of the compounds of the invention, the Ullman ether synthesis, also has limitations. The groups R_6-R_9 on the phenol should be electron donating and the groups on the bromide **6** should preferably be electron withdrawing (Kunz, K.; Scholz, U.; Ganzer, D. *Synlett*, **2003**, 2428-2439, pg.). As stated in recent review on such couplings: "The only restriction, which applies to almost all following procedures as well, is the need for electron rich or at least electron neutral phenols." Of course the reactions

they were speaking of require optimization of the catalyst, ligand, and solvent and are generally not conducted in microwave at 220°C. It is also worth mentioning that amines can undergo coupling with aryl bromides, where "NR_ZR_W-C_{1-6}-alk(en/yn)yl" (Kunz, et. al. ibid. 2833 Table 1). Cu(I) salts also have a rich chemistry with alkynes and a recent review summarizes major aspects (Siemensen et. al. *Angew. Chem. Int. Ed.* **2000** *39*, 2632-2657). If the acetylene is terminal copper acetylides will be formed. The Cadiot-Chodkiewicz coupling will occur between " halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy" and "C1-6-alk(en/yn)yl, C1-6-alk(en/yn)yloxy, C1-6--alk(en/yn)ylsulfanyl, hydroxy-Cl-6--alk(en/yn)yl, halo-C1-6-alk(en/yn)yl, halo-C1-6--alk(en/yn)yloxy, Cl_6-alk(en/yn)yl, cyano-Cl.8-alk(en/yn)yl, C3_8-cycloalk(en)yl, C3-8-cycloalk(en)yl-Cl_s-alk(en/yn)yl, and NR_ZR_W-Cl.s-alk(en/yn)yl, wherein Rz and Rw are independently Cl.8-alk(en/yn)yl, C3-8- cycloalk(en)yl, and C3.8-cycloalk(en)yl-Cl.s-alk(en/yn)yl" (Kunz, ibid. pg. 2635).

As per the MPEP:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

A) The claims are very broad. B) The invention is directed to chemical compounds which must be synthesized. C) The prior art teaches that the methods disclosed cannot be used to synthesize the scope of the invention. D) One with a BS degree in chemistry would recognize the limitations listed above. E) Chemistry is an unpredictable art (*In re Marzocchi*, 169 USPQ 367, *In re Fischer*, 166 USPQ 18). F) The inventor provides no direction for many of the substituents listed. The conditions are extreme boiling in acid, temperatures of 220°C. G) There are very few working examples: except these substituents, in very specific positions: OMe, Cl, F, Me, Cl, CH_3, CF_3.

The MPEP states in 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

8. Claims 18, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 33 of the disclosure "Results of the experiments showed that the tested compounds of the invention inhibit the norepinephrine and serotonine [sic] reuptake with IC_{50} below 200nM". Is this for both assays for all compounds? The examiner finds it incredulous that all the millions of compounds claimed have this dual-activity. Applicant seems to believe that these compounds are useful for "treating affective disorders". One "affective disorder" that applicant has claimed is depression. In a recent review on the subject of monoamine reuptake inhibitors (Thorsten et. al. *Drug Discovery Today* **2004**, 1(1) 111-116, pg. 138) states:

> " Whether novel monoamine reuptake inhibitors with different monoamine ratios would give a better efficacy is still not known. Hitherto, the least evaluated option is a combination of 5-HT, NA, DA and monoamine reuptake inhibition. This combination could give an accelerating treatment response or increased efficacy in otherwise treatment-resistant depressed patients. An elimination of SSRI-like side effects might be possible, although the risk for DA related side effects should be considered. Large conclusive clinical trials will be the only option to guide further drug discovery of monoamine transporters."

The examiner wonders what the effects on dopamine transport are, as this could play a major role in the clinical application. The similarity of these compounds to cocaine, make these compounds liable for abuse, and few physicians would argue that cocaine, while elevating mood, is a good treatment for depression or affective disorders. In addition, procaine, a local anesthetic, is known to inhibit monoamine uptake using assays similar to the ones described (Sato, et. al. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *361*, 214-220, entire document), yet it has not been shown to be efficacious for the treatment of depression or anxiety disorders, and one would have

serious doubts that a medical doctor would use procaine in such a manner. Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Applicant claims that these compounds are useful for "anxiety disorders". However a recent review (Milan, M. J. *Progress in Neurobiology* **2003**, *70*, 83-244 pg. 13) states:

> "With one exception in mice (Hascoët et al., 2000), acute administration of SSRIs or 5-HT/NA reuptake inhibitors **has proven to be ineffective or to increase anxiety** in the VCT and other conflict procedures, mirroring above-mentioned clinical and experimental observations (Table 16 and Fig. 7) (Mason et al., 1987; Fontana and Commissaris, 1988; Fontana et al., 1989a; Kostowski et al., 1994; Beaufour et al., 1999; Borsini et al., 2002). In certain conflict paradigms, it has been shown that chronic treatment is accompanied by the progressive induction of anxiolytic effects (Fontana and Commissaris, 1988; Fontana et al., 1989a; Beaufour et al., 1999; Borsini et al., 2002) and, assuming its appropriate manipulation to detect acute anxiogenic actions of SSRIs and 5-HT/NA reuptake inhibitors, such studies would be of interest to undertake with the VCT."

Thus this seems to say that at least in animal models compounds with the same purported mechanism cause anxiety. Furthermore it is not clear, what these compounds will do in such complex disease states, and one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of claims 18, 32-34. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re

Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). Even if a correlation existed between the pharmacological activity alleged and a clinical manifestation, we have only *in-vitro* testing of these compounds and no *in-vivo* data. Without at least animal studies of *in-vivo* activity one cannot believe that these compounds will behave as therapeutics in those suffering from depression/anxiety disorders. It seems very unlikely that a medical doctor would know what to do with these compounds. Given the mechanism that applicant alleges and the current knowledge in the art no method of use is enabled. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the"..."claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this invention that has no working examples in this unpredictable art without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-15, 18, 20-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliot et. al. PCT/IB00/00108. The factual inquiries set forth in

Graham **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Elliot et. al. disclose 2-[2-(3,4-dichlorophenoxy)-5-flurophenyl]-piperidine **I** on pg. 9 line 13, which has the same utility of the instant case (inhibition of monoamine reuptake); shown side-by-side with applicant's structure **II** in Figure 2.

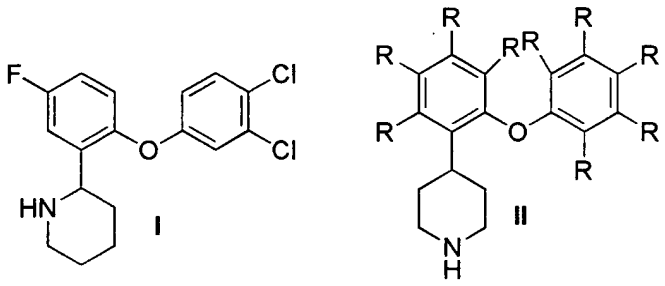


Figure 2. Compounds of the instant case vs. those of Elliot et. al.

These are clearly position isomers. The compounds of Elliot et. al. PCT/IB00/00108 are 2-aryloxy-piperidines and those of the instant case are 4-aryloxy-piperidines. The only difference here is the position of the biaryl ether on the piperidine ring (2 in the '108 application and 4 in the instant case). One of ordinary skill in the art is one with experience in medicinal chemistry and pharmacology and knows the basics of drug design. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on

the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency. The applicant would have been motivated to make the change based on the fact that 4-aryl-piperidines were well known in the art to have the desired monoamine reuptake activity as evidenced by numerous publications: (Wang S., et. al. *J. Med. Chem.* **2000**, *43*, 351–360. Tamiz A.P, et. al. *J. Med. Chem.* **2000**, *43*, 1215–1222. Sakamuri S, et. al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495–500.). The opinion set forth in 16 USPQ2d *1897 In re Dillon U.S. Court of Appeals Federal Circuit No. 88-1245 Decided November 9, 1990 919 F2d 688*: "When chemical compounds have 'very close' structural similarities and similar utilities, without more a prima facie case may be made." In the instant case the structure is very similar and the utility is the same, thus the claims at hand of the instant case (1-15, 18, 20-34) are obvious over the prior art. Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ullyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments]

do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...".

Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* ($CONH_2$) and *ortho* (OCH_3) obvious over a dye with the

same nucleus and *meta* ($CONH_2$) and *para* (OCH_3) group), *Ex parte Allais*, 152 USPQ 66, (3-aminopropyl-6-methoxyindole obvious over a reference teaching 3-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene).

Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound

may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

10. Claims 1-16, 18, 20-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et. al. *J. Med. Chem.* **1979**, *22*, 1347-1354 in view of Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action* 1992, Academic: New York, pg 19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) Martin et. al teach 2'-benzyl-4-phenyl-piperidines bearing a variety of *p*-substituents in the benzyl moiety (F, OMe, OH, H) and a 2'-benzyl-4-phenyl-tetrahydropyridine that are active antidepressants Martin et. al. *J. Med. Chem.* **1979**, *22*, 1347-1354 . The piperidines are labeled **9a**, **9d-9f** and are shown in Table I pg. 1349. The 2'-benzyl-4-phenyl-tetrahydropyridine prepared is listed as compound **6h** Table III, pg 1350. In this case the assay was an animal behavior model of depression where tetrabenazine mediated effects were alleviated with the test compounds. While antagonism of the effects of tetrabenazine may proceed through a mechanism other than monoamine reuptake, the authors were careful to evaluate these compounds in a rat brain synaptosome norepinephrine reuptake inhibition assay with compound **9a** and confirm

the mechanism. Moreover the overall study teaches us something more about the general picture of activity in this compound series:

> Antitetrabenazine structure-activity relationships for piperidines **7-9** and **11** (Table I) are generally similar to relationships observed with the 3-arylspiro[isobenzofuran-l(3H),4'-piperidine.S3]* 4 Thus, optimal activity appears to be associated with analogues where the nitrogen substituent is a hydrogen **(9a)** or a small alkyl group **(7a).** A larger nitrogen substituent **(7g** vs. **7a)** and N-hydroxylation **(11** vs. **9a)** lead to reduced activity. A basic nitrogen appears to be required for activity, **as** carbamate **8a** is essentially inactive. Significant antitetrabenazine activity is associated only with derivatives in which the phenylmethyl moiety is *ortho* rather than meta or para with respect to the piperidine ring **(7a** vs. **7b,c; 9a** vs. **9b,c).** Selection of aromatic substituents (F, OCH_3, and OH) was based on the observed activity of the corresponding **3**-arylspiro[isobenzofuranl(3H) ,4'-piperidines]. Tertiary amine derivatives with these substituents **(7d-f)** display reduced antitetrabenazine activity in comparison with **7a,** whereas the activity of secondary amine analogues is equipotent **(9d),** decreased **(9e),** and slightly enhanced **(9f)** in comparison with **9a.** The fact that an aromatic substituent frequently does not influence antitetrabenazine activity of tertiary and secondary amines in a similar manner was also reported for 3-arylspiro[isobenzofuran-1(3H),4'-piperidines]. Piperidines **7a** and **9a,d,f** display antitetrabenazine activity comparable to imipramine or amitriptyline but are two to fourfold less potent than the analogous 3-arylspiro-[isobenzofuran-l(3H) ,4'-piperidines]. Piperidinols **3,** esters **4,** and ethers **5** (Table **II)** generally display weak antitetrabenazine activity, with the exception of **3d,h** and **5c** which exhibit modest activity. Benzyl ethers **13** (Table **IV),** at best, display modest activity, with tertiary amine **13d** being approximately twice as potent as secondary amine **13a.** Tetrahydropyridines **6** (Table **III)** also, at best, exhibit modest activity, with the exception of secondary amine **6h** which is comparable to amitriptyline.

They teach that *ortho* substitution of the benzyl moiety is preferred, and that compounds **6h**, **9a**, **9d-9f** are preferred compounds. In addition the authors state that "the fact that an aromatic substituent frequently does not influence antitetrabenazine activity of

tertiary and secondary amines" which leads us to believe that the substituents on the aromatic ring are not important for activity.

Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action* 1992, Academic: New York, pg 19, teaches that "*Bioisosteres* are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties." He goes on to state Erlenmeyer's 1948 definition of "classical isosteres" as "atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical". Table 2.2 lists several of these classical isosteres under heading 2, it is clear that the ether linkage (-O-) is a classical bioisostere of methylene ($-CH_2-$).

B) The only difference between the compounds of the instant case and those of Martin et. al is the bioisosteric replacement of methylene $-CH_2-$ with an ether linkage (-O-). These compounds are shown side-by-side in Figure 3, for clarity.

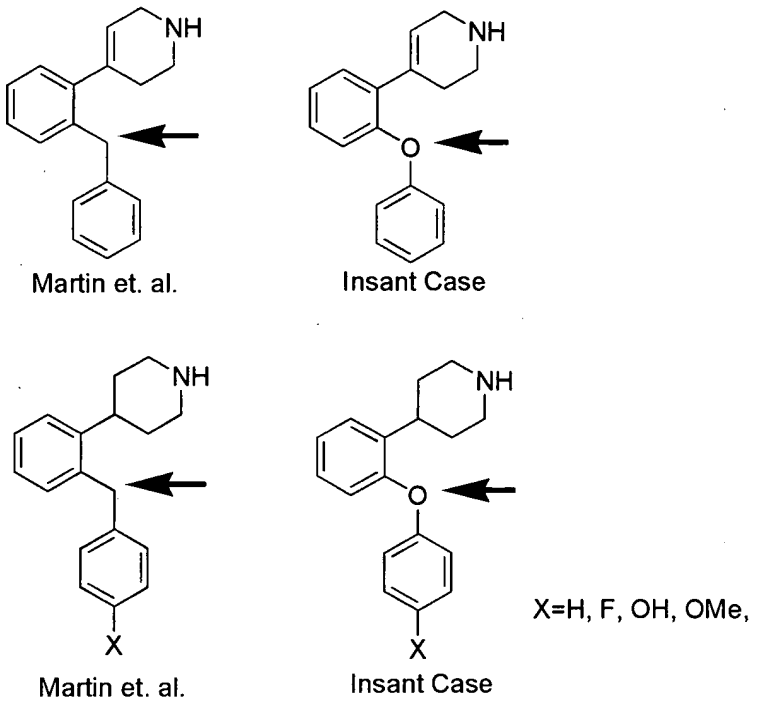


Figure 3. Isosteric Replacement of CH_2 with O in the compounds of Martin et. al.

The other species claimed, differ only in the substituents in the aryl ring.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these bioisosteres based on the expectation that such bioisosteres would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. Moreover Elliot et. al. PCT/IB00/00108 teaches that biaryloxyethers with a 2-piperidine moiety (Figure 2, structure **I**) are effective monoamine reuptake inhibitors. Thus this piece of information provides a strong motivation to make the change and one skilled in the art could expect an increase in potency in going from the methylene to O

linkage. The courts have examined obviousness in a very similar situation *Mead Johnson & Co. v. Premo Pharmaceutical Labs* **207** USPQ 820-852, where a bioisosteric replacement of methylene (CH2) with oxygen (O) was the issue and held that oxygen substituted compound Isoxsuprine was obvious over Nylidrin the methylene prior art compound, (Figure 4).

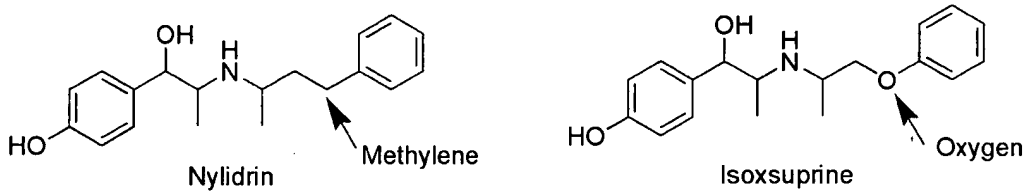


Figure 4. Compounds of *Mead Johnson & Co. vs. Premo Pharmaceuticals* 207 USPQ 820 (pg.825).

Here we have the prior art which teaches a very narrow set of compounds with the same utility. The modification [(CH_2) to (O)] was well known in the same very specific art and was the preferred or at the very least an alternative substituent. Thus a finding of obviousness is appropriate in this case.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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